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Asymmetric Autocatalysis as a Relay for Remote Amplification of Chirality of Target Molecules Used as Triggers

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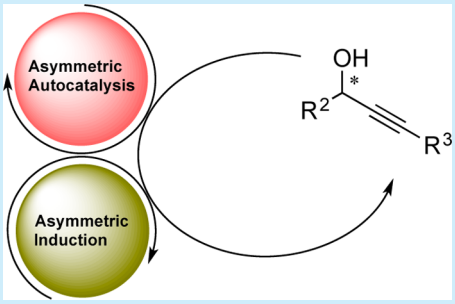
Supporting Information

ABSTRACT: Nearly racemic target molecules are enantiomerically enriched through an asymmetric autocatalytic relay for a remote amplification of chirality. Target alkynols with very low initial ee act as chiral triggers for asymmetric amplification of the Soai autocatalyst, which in turn enables the formation of the same alkynols with greater enantiomeric purity. Additionally, the stereochemical correlation between the trigger/target and autocatalyst molecules is discussed.



The chiral homogeneity of biomolecules is considered to be directly related to the origin and evolution of life and continues to fascinate scientists.[1] Homochirality might have preceded the origin of life, but it remains intriguing how and when biomolecules achieved high enantioenrichment. Once generated, even with a small imbalance, complex chemical systems are required for amplification and propagation of homochirality.[2] In this context, asymmetric autocatalysis is particularly interesting; as such, a chemical system may combine self-replication with amplification of chirality. However, addressing this matter with direct autocatalytic processes is far from obvious for most chemical reactions. Alternatively, a nonenzymatic bias would provide a platform toward one absolute sense of chirality.

Herein, we describe an unprecedented remote amplification of chirality by taking advantage of the singularity of asymmetric autocatalysis. The Soai reaction offered the first, and to date the only, example of an asymmetric autocatalytic reaction to provide spectacular chiral amplification.[3] It is described as a Frank-like[1a] reaction network operating in a closed system to give rise to absolute asymmetric synthesis under kinetic control with nonlinear amplification of ee.[4] Remarkably, this reaction is highly responsive to discrete chiral external stimuli prior to initiation of the reaction, such as surfaces of inorganic crystals[5] and circularly polarized light.[6] In other responsive chiral catalytic systems reactivity or selectivity can be modulated by external signals.[7] However, this chirality is already within the described catalysts. Perhaps more interesting, chiral compounds including alcohols, amino acids, epoxides, and $[Cr(acac)_3]$ can serve as external stimuli to induce asymmetric autocatalysis of **1**.[6a,8]

As such, the reaction is an extremely sensitive qualitative sensor for chirality and therefore can be considered as a tool for a "read in" of a tiny optical activity. Besides, inspired by the work of Soai et al., we recently reported that autocatalyst **1**, generated from **2**, was also able to propagate the amplified chirality, which can be considered as a "read out" for transfer of chirality to other alkanols and alkynols from azaaryl aldehydes **4**−**7**.[9,10] This observation offers opportunities toward the design of responsive chemical systems by a judicious choice of sequences of chemical reactions, one of which could be an asymmetric autocatalytic reaction as the bias.

The proposed functioning of such a chemical system offers a complementary model for homochirality to rise and become ubiquitous without chiral templates, as illustrated in Figure 1.

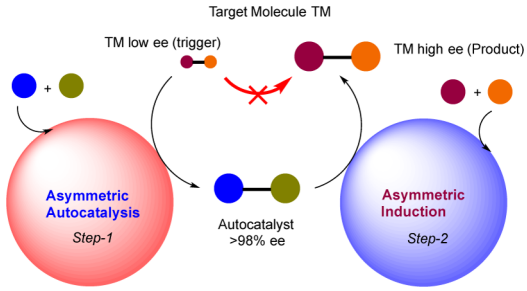


Figure 1. Strategies toward remote self-replication.

The overall process enables copy catalysis of stereochemical information, chirality, with improved enantiopurity. We demonstrate that a chiral target molecule **TM**, the external signal, is able to trigger asymmetric amplification of autocatalyst Zn−**1** that operates as a chiral relay generated in situ by role conversion from product to catalyst, propagating chirality in newly formed **TM**. In other words, a *nearly racemic target molecule would be able to trigger the formation of its own chiral catalyst for remote amplification of chirality.*

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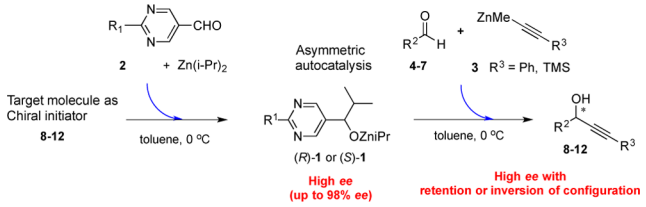
To exemplify the basic principles described above, we noted the advantage of alkynols **8**−**12** as target molecules in the designed chemical system, as a model reaction, because they are not capable of asymmetric amplification. The example depicted in Scheme 1 illustrates a general protocol where a target chiral

Scheme 1. General Protocol for Remote Amplification of Alkynols 8−**12**



alcohol **8**−**12** with enantiopurity as low as 2% ee could be amplified remotely. Thus, in the first step, 0.2 mol % of molecule **8**−**12** triggers the asymmetric amplification of the Soai autocatalyst Zn−**1** to reach >98% ee. In the second step, Soai autocatalyst induces (catalyzes) the formation of the target alkynol **8**−**12** from its precursors.

However, the chiral sign may be dependent upon that of the chiral initiator. Thus, the resulting process may lead to opposite absolute configuration along the course of asymmetric amplification. Shibata et al. have previously reported the correlation of absolute configuration of initiator and Soai alcohol.[11] Therefore, before carrying out the remote enantioselective amplification reactions, the correlation between the absolute configuration of the chiral propargylic alcohols and the pyrimidyl alkanol has to be established and may be quantified too.

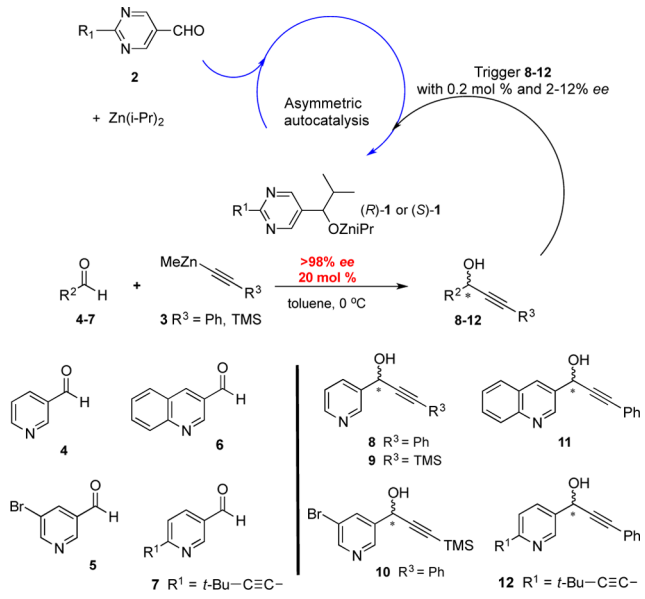
We began our investigations by examining the asymmetric autocatalytic amplification of the pyrimidyl alkanol **1** in the presence of the trigger/target molecule (or chiral initiator, as named by Soai et al.). Preliminary experimentation revealed that starting with (*S*)-pyridyl alkynol **8** at 64% ee, autocatalytic amplification of (*S*)-pyrimidyl alkanol **1** was observed up to 88% ee. Thus, pyridyl alkynol **8** is able to trigger the amplification of alkanol **1**. Surprisingly, as we could notice, the absolute configuration of product **8** obtained through this process was opposite to the absolute configuration of the trigger molecule of the same chemical structure, i.e., its enantiomer.

For example, it is Soai's autocatalyst (*R*)-pyrimidyl alkanol **1** which induces formation of (*S*)-pyridyl alkynol **8**. Thus, it is reasonable to expect this stereochemical relationship to be retained during the trigger step; i.e., (*S*)-**8** would initiate autocatalysis of (*R*)-**1**. A similar reversal phenomenon has been observed for Soai autocatalysis with other chiral initiators.[12] In fact, the reversal phenomenon observed here occurs during the trigger step and could be interpreted as a consequence of a difference between the two reactions involved in this chemical system, i.e., alkylation vs alkynylation. These two reactions would proceed through distinct mechanisms as a result of interactions between zinc alkoxides aggregates, which form the catalytically active species. However, it was proposed that the correlation of absolute configuration could be analyzed on the basis of the bulkiness of various substituents in trigger molecules.[11]

This result was encouraging as it provides evidence for the functioning of the remote amplification of chirality, although with inversion of configuration. Therefore, we set out to examine the structural features that could allow retention of configuration as well as the extent of the asymmetric amplification from very low initiator ee in these coupled chemical systems. Thus, formation of **1** through autocatalytic amplification was subjected to the external chiral stimulus of various chiral alkynols **8**−**12**. Withdrawn samples were used to monitor product formation, and enantiomeric ratio and absolute configurations of product **1** and **8**−**12** were determined by chiral HPLC. For further experimental details, see the Supporting Information.

Initially, the amplification process was carried out as illustrated in Scheme 2, with chiral trigger/target compound

Scheme 2. Remote Asymmetric Amplification of Alkynols 8−**12**



8−**12** with ca. 10% ee and aldehyde **2** (catalytic amount) in the presence of *i*-Pr$_2$Zn in toluene at 0 °C. This way, high amplification of chirality ensued after three to four autocatalytic cycles to reach nearly enantiopure values of >98% ee for product **1**. Subsequently, the resulting mixture was added to a solution of alkynylzinc reagent **3** followed by addition of aldehyde **4**−**7**.

(*R*)-Pyridyl alkynol **8** was used as chiral source with 8% ee to induce asymmetric autocatalysis of (*R*)-**1**. Analyses of the reaction mixture revealed that (*R*)-**1** was amplified to 95% ee after four consecutive autocatalytic cycles and then added to a solution of alkynylzinc reagent **3** followed by addition of aldehyde **4**. In response, the (*R*)-**1**-catalyzed alkynylation reaction provided 84% of (*S*)-product **8** with 67% ee (Table 1, entry 1). It should be noted that again this reaction sequence proceeded with inversion of configuration from trigger to product molecules. Similarly, when asymmetric amplification of (*R*)-**1** (98% ee after three cycles) was triggered by (*S*)-**9** with 10% ee, reversal occurred to provide the opposite configured (*R*)-**9** with 82% ee (Table 1, entry 2).

Using quinoline or substituted pyridine as trigger/target molecule resulted in improved remote amplification. Indeed, compound (*R*)-**11** with 10% ee was able to catalyze its own remote amplification affording an excellent yield of 84% with 67% ee (entry 4). Interestingly, during this reaction sequence,

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Table 1. Remote Asymmetric Amplification of Triggers 8−12 through Soai Asymmetric Autocatalysis of 1

					products **8−12**	
entry[a]	ald	chiral trigger	trigger's initial ee	abs conf **1**	% yield[b]	% ee[c] (conf)[d]
1	4	(*R*)-**8**	8	*R*	84	67 (*S*)
2	4	(*S*)-**9**	10	*R*	74	82 (*R*)
3	5	(S)-**10**	12	*R*	58	84 (*R*)
4	6	(*R*)-**11**	10	*R*	86	67 (*R*)
5	7	(*R*)-**12**	11	*R*	83	68 (*R*)
6	4	(*S*)-**8**	2	*S*	88	68 (*R*)
7	7	(*S*)-**12**	2	*S*	88	71 (*S*)

[a]Reactions were carried out under nitrogen. The molar ratio in the amplification step of chiral trigger-aldehyde **2**- *i*-Pr_2Zn = 0.01:1:1.4. [b]Isolated product after column chromatography. [c]ee values were determined by HPLC analysis. [d]Absolute configuration was determined by analysis of the corresponding Mosher ester ^{1}H NMR spectrum.

formation of the (*R*) enantiomer of autocatalyst **1** was observed, showing consecutive retention of configurations. In an analogous reaction sequence, the target compound (*R*)-**12** with an initial 11% ee amplified significantly by remote replication to 68% ee (entry 5). Here again, the chiral relay (*R*)-**1** was identified during the replication process.

Finally, the reliability of this chemical system in remote amplification of chirality was confirmed in translating very low initial ee of trigger compounds. Figure 2 reveals the remarkable

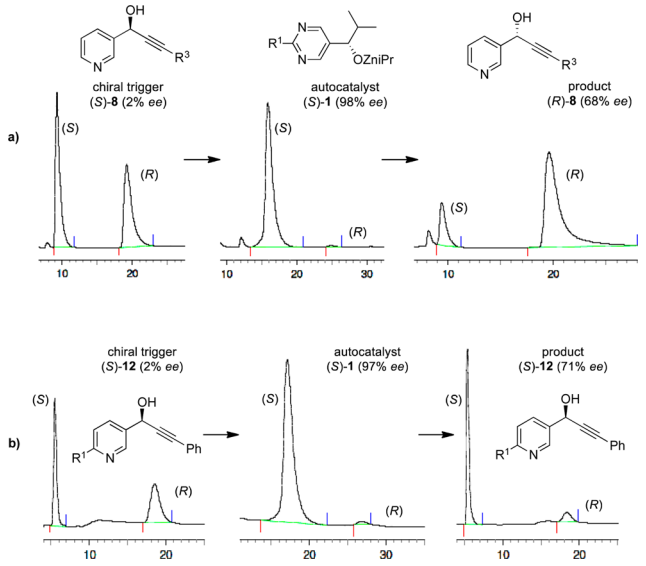

Figure 2. (a) Remote amplification of chirality with inversion of configuration and (b) with retention of configuration.

amplification of autocatalyst (*S*)-**1** to >98% ee triggered by 0.2 mol % of chiral target alkynols (*S*)-**8** or (*S*)-**12**, initially with ca. 2% ee, into enantioenriched molecules as depicted in Table 1 (entries 6 and 7). Under identical conditions, enantiomer (*R*)-**8** amplified to 68% ee at the expense of trigger (*S*)-**8** (Figure 2a), while (*S*)-**12** improved itself notably to 71% ee (Figure 2b).

The autocatalytic amplification of **1** was examined as a function of the structure and chirality of the chiral trigger compound, as shown in Figure 3. Examination of this plot reveals a clear structure dependence of asymmetric amplification of **1** for the first autocatalytic cycles. Indeed, (*R*)-**8** (8% ee)

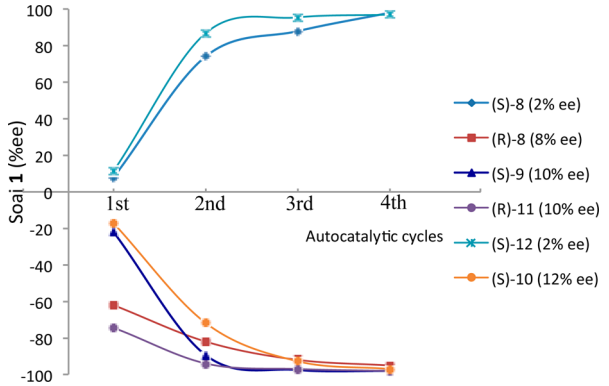

Figure 3. Amplification of Soai autocatalyst triggered with chiral seeds **8−12**.

and (*R*)-**11** (10% ee) prompted remarkable amplification of (*R*)-**1** to 62% and 74% ee within only the first cycle, respectively.

In contrast, starting with similar initial ee, (*S*)-**9** and (*R*)-**10** were only capable of triggering amplification of (*R*)-**1** in the range of 17−22% ee. Notice that lower initial ee of the trigger molecule also results in low amplification in the first cycle as, for example, in the case of (*S*)-**8** (2% ee). Interestingly, higher levels of enantiopurity of **1** in the range of 72−94% ee are reached with all trigger molecules **8−12** after the second autocatalytic cycle. The most significant amplification of **1** was observed in the case of (*S*)-**8** with 11% ee after the first autocatalytic cycle to increase up to 87% ee after the second cycle.

The present study described a responsive chemical system for a two-way communication of chirality with amplification of ee. A target organic molecule with low ee, or nearly racemic, is used as a chiral inducer/trigger of asymmetric autocatalysis that can be translated into the remote asymmetric amplification of the target molecules by use of Soai's autocatalyst. Thus, chiral information is restored with amplification to deliver a copy of the target molecule with high fidelity, although high amplification is also observed with opposite absolute configuration for other substrates. Additionally, the latter can be considered as amplification of minor enantiomer. This is not necessarily a drawback for the present concept; this observation reminds us of the challenging complexity in communicating chirality as chemical information. As such, the results presented here provide a new concept to make homochirality ubiquitous and offer a first demonstration of a responsive chemical system for a remote amplification of chirality by read-in and read-out of chiral information from an external trigger using an autocatalyst, generated in situ, as a chiral bias.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00742.

Detailed experimental procedures, ^{1}H and ^{13}C NMR spectra, and other characterization data for the materials (HPLC, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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